Modified Augmented Renal Clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients

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BACKGROUND: Recent evidence suggests that current antimicrobial dosing may be inadequate for some critically ill patients. A major contributor in patients with unimpaired renal function may be Augmented Renal Clearance (ARC), wherein urinary creatinine clearance exceeds that predicted by serum creatinine concentration. We used pharmacokinetic data to evaluate the diagnostic accuracy of a recently proposed ARC score.

METHODS: Pharmacokinetic data from trauma/surgical intensive care unit patients receiving piperacillin/tazobactam were evaluated. We combined intermediate scores (4–6 points) into a single low score (≤6) group and compared pharmacokinetic parameters against the high (≥7) ARC score group. Diagnostic performance was evaluated using median clearance and volume of distribution, area under the antibiotic time-concentration curve (AUC), and achievement of free concentrations greater than a minimum inhibitory concentration (MIC) of 16 μg/mL for at least 50% of the dose interval ($fT > MIC \geq 50\%$). Alternative dosing strategies were explored in silico.

RESULTS: The ARC score was 100% sensitive and 71.4% specific for detecting increased clearance, increased volume of distribution, decreased AUC, and $fT > MIC < 50\%$ at an MIC of 16 μg/mL. The area under the receiver operating characteristic curve was 0.86 for each, reflecting a high degree of diagnostic accuracy for the ARC score. Serum creatinine less than 0.6 mg/dL had comparable specificity (71.4%) but was less sensitive (66.7%) and accurate (area under the receiver operating characteristic curve, 0.69) for detecting higher clearance rates. Monte Carlo pharmacokinetic simulations demonstrated increased time at therapeutic drug levels with extended infusion dosing at a drug cost savings of up to 66.7% over multiple intermittent dosing regimens.

CONCLUSION: Given its ability to predict antimicrobial clearance above population medians, which could compromise therapy, the ARC score should be considered as a means to identify patients at risk for subtherapeutic antibiotic levels. Adequately powered studies should prospectively confirm the utility of the ARC score and the role of antimicrobial therapeutic drug monitoring in such patients. (*J Trauma Acute Care Surg*. 2014;77: S163–S170. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic tests, level III.

KEY WORDS: Augmented Renal Clearance; ARC score; sensitivity and specificity; antimicrobial pharmacokinetics and pharmacodynamics; trauma critical care.

Mortality among intensive care unit (ICU) patients remains high despite numerous clinical and technologic advances supporting the care of critically ill patients. Sepsis continues to be a leading cause of mortality in this population, prompting the dissemination of clinical guidelines in conjunction with an international campaign dedicated to improve outcomes.[1,2] In the era of multiply drug-resistant pathogens and rising antimicrobial minimum inhibitory concentrations (MICs), there is increasing emphasis on the optimization of antimicrobial dosing by applying pharmacokinetic (PK) and pharmacodynamic (PD) principles to antimicrobial therapy to improve outcomes.

Younger individuals who experience trauma generally have disease-free organs with the potential to clear drugs with great efficiency. Recently, the phenomenon of Augmented Renal Clearance (ARC) has been described, wherein glomerular filtration measured by the urinary creatinine clearance significantly exceeds what is predicted by the serum creatinine concentration according to various mathematical equations.[3] This is thought to result from an increase in cardiac output; however, invasive monitoring found this not to be associated with ARC.[4] Regardless of the cause, ARC is thought to result in more rapid elimination of renally cleared medications and has been shown to compromise the PK/PD efficacy of β-lactam antibiotics.[5]

A recent study identified risk factors for ARC to be age of 50 years or younger, trauma, and Sequential Organ Failure

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Assessment (SOFA) score of 4 or less.[4] This aptly describes the majority of expected combat trauma patients based on military demographics[6] and many critically injured civilian patients. The ARC score was implemented as the weighted odds ratios derived from logistic regression of subjects exhibiting enhanced urinary creatinine clearance (≥130 mL/min). The study was limited in that PK parameters were not measured for direct correlation to the ARC score, and external validation is lacking.

In two observational studies ongoing at our facility ex amining antimicrobial pharmacokinetics, we have noted unusually high clearance rates of renally cleared antibiotics, which tend to occur more often in younger, critically ill individuals. We considered that this might be caused by ARC occurring in these individuals and hypothesized that the ARC score may identify individuals with higher antibiotic clearance rates and subtherapeutic plasma levels. To test this hypothesis, we applied the ARC risk score to surgical and trauma ICU patients with normal renal function who provided PK data for piperacillin/tazobactam. This allowed comparison of the PK parameters of each group and thus an evaluation of the diagnostic performance of the ARC score in a real-world setting.

PATIENTS AND METHODS

Study Design and Subjects

We performed a cross-sectional study comparing two groups of patients from a pooled cohort of subjects enrolled in two prospective, observational PK studies at Brooke Army Medical Center, Fort Sam Houston, Texas. One study examined antimicrobial PK in critical illness (nine subjects), while the other examined antimicrobial PK in the setting of negative-pressure wound therapy (four subjects). Subjects were enrolled between October 1, 2012, and September 30, 2013. Subjects were eligible if they were 18 years or older, admitted to the surgical or trauma ICUs 72 hours from injury or longer, and treated with intermittent doses of piperacillin/tazobactam. Exclusion criteria were pregnancy or detention by law enforcement. Written consent was obtained from subjects or their legally authorized representatives. Approval was obtained from the institutional review boards of the US Army Medical Research and Material Command and the San Antonio Military Medical Center. As glomerular hyperfiltration is unlikely in the setting of renal impairment, subjects were excluded if the estimated glomerular filtration rate was less than 90 mL/min per 1.73 m^2 as determined by the four-variable Modification of Diet in Renal Diseases equation, which is automatically reported in the patient record in our facility.

ARC Score

The ARC scoring system, as originally described,[4] allocates points for age of 50 years or younger (6 points), trauma (3 points), and SOFA score of 4 or less (1 point). To contrast those at highest risk for ARC from other individuals, the ARC score was modified such that subjects in the originally described intermediate category (4–6 points) were allocated to the low-score group (thus defined as 0–6 points). ARC scores were calculated using the subjects' SOFA scores on the date of PK sampling and applied after all PK parameters had been determined. The diagnostic performance of the modified ARC score was characterized using standard definitions of sensitivity, specificity, as well as positive predictive value (PPV) and negative predictive value (NPV). Predictive accuracy was assessed with the area under the receiver operating characteristic (ROC) curve, using population medians for clearance (mL/kg/min), volume of distribution (L/kg), area under the time-concentration curve (AUC) (μg·h/mL), and $fT > MIC$ (for MIC of 16 μg/mL) as threshold values in this analysis. Thus a "true positive" would be reflected by a high ARC score with clearance and volume of distribution greater than and AUC and $fT > MIC$ less than the median value for the overall population.

PK Sampling

Undiluted whole blood samples were obtained before dosing and at five or six prespecified sampling times after infusions, depending on the dose interval. Whole blood samples were collected in EDTA-containing phlebotomy tubes. Doses were selected at the discretion of treating clinicians. Blood samples were immediately centrifuged at 1,000 G, at 4°C for 10 minutes, and the plasma was separated and stored at −80°C until analysis.

Sample Analysis

Total concentrations (i.e., protein-bound plus protein-unbound) of piperacillin and tazobactam were determined in plasma samples by high-performance liquid chromatography (HPLC) by a single trained analyst (K.L.N.). Free fractions (i.e., unbound only) of each drug were isolated by ultrafiltration. HPLC was performed with a Dionex 3000 HPLC system (Dionex, Thermo-Fisher Inc., Sunnyvale, CA) with UV detection, and free and total drug concentrations were quantified according to separate calibration standards. Complete experimental details are provided in the Supplemental Methods (http://links.lww.com/TA/A408).

PK/PD Analyses

Parameters describing the disposition of free drug fractions were estimated for each patient by noncompartmental analysis using WinNonLin version 6.3 (Pharsight Inc., Sunnyvale, CA). The therapeutic response function of the software was used to determine the percentage of time during which the free piperacillin concentrations remained greater than the theoretical bacterial MICs ($fT > MIC$). Free piperacillin concentrations greater than the MIC for at least 50% of the dose interval ($fT > MIC \geq 50\%$), which predicts optimal bacterial killing by piperacillin, were selected as the relevant PK/PD target value. MIC values of 1, 2, 4, 8, 16, 32, and 64 μg/mL were selected because they span the susceptible (16 μg/mL) and intermediate (32 μg/mL) breakpoints (Clinical and Laboratory Standards Institute, Wayne, PA) for the *Enterobacteriaceae* and *Pseudomonas aeruginosa*, which are frequent pathogens of critically ill patients who often can be treated with piperacillin/tazobactam.

Probabilities of target attainment for current and alternative piperacillin dosing strategies were explored by conducting a 10,000-subject Monte Carlo simulation for each dose using Crystal Ball software (Oracle, Redwood Shores, CA) using the log-normal distributions for clearance and volume of distribution parameters calculated from patients with high or low ARC scores. Since standard piperacillin/tazobactam doses of 2.25,

TABLE 1. Characteristics of Study Subjects Receiving Piperacillin/Tazobactam Included in This Study

Subject	Age, y	Sex	Mechanism	Indication	Dose*	eGFR**	SOFA†	APACHE II‡	ARC Score§	Outcome
1	44	F	Surgical complication	Intra-abdominal infection	3.375 g every 6 h	202.3	4	15	7	Clinical cure
2	47	M	MVC	Sepsis	3.375 g every 6 h	100.7	7	12	9	Clinical cure
3	62	M	MVC	GNR bacteremia	4.5 g every 6 h	98.0	2	7	4	Clinical cure
4	25	M	Intestinal volvulus	Intra-abdominal abscess	3.375 g every 6 h	97.8	2	8	7	Clinical cure
5	20	M	MVC	Sepsis	4.5 g every 6 h	178.6	6	15	9	Clinical cure
6	57	F	Small bowel obstruction	Suspected VAP	3.375 g every 6 h	198.5	5	18	0	Clinical cure
7	38	M	MVC	GNR VAP	4.5 g every 6 h	130.5	8	25	9	Clinical cure
8	24	M	Surgical complication	Intra-abdominal abscess	4.5 g every 6 h	134.1	4	19	7	Persistent abscess
9	43	F	MVC	Suspected VAP	4.5 g every 6 h	190.6	6	10	9	Clinical cure
10	50	M	MVC	Open fracture	3.375 g every 6 h	103.0	8	20	9	Limb amputation
11	25	F	Surgical complication	Intra-abdominal infection, sepsis	3.375 g every 6 h	189.0	6	14	6	Clinical cure
12	83	F	MVC	Bowel necrosis	3.375 g every 6 h	95.5	10	21	3	Clinical cure
13	63	M	Oncologic complication	Mandibular osteomyelitis	3.375 g every 6 h	90.6	4	15	1	Clinical cure

*Dose of piperacillin/tazobactam.
**eGFR (mL/min/1.73 m^2) calculated using the Modification of Diet in Renal Diseases equation.
†SOFA score on the day of sampling.
‡APACHE II score on the day of sampling.
§Modified ARC score, sum of age of 50 years or younger (6 points), trauma (3 points), and SOFA score of 4 or less (1 point).
eGFR, estimated glomerular filtration rate; GNR, gram-negative rod; MVC, motor vehicle collision; VAP, ventilator-associated pneumonia.

3.375, and 4.5 g include 0.25, 0.375, or 0.5 g of tazobactam, a β-lactamase inhibitor, only the piperacillin doses were considered for alternative dose administration. Modeled doses included 30-minute infusions of 2, 3, 4, or 6 g given every 4 hours; 4-hour infusions of 3 or 4 g given every 6 or 8 hours; 30-minute infusions of 6 or 8 g given every 6 or 8 hours; or continuous infusion total daily doses between 12 g/d and 24 g/d. In addition, the impact of ARC on standard 30-minute infusions of 3 g and 4 g every 6 hours was explored. Predicted free piperacillin concentration was calculated as 60.2% of the total piperacillin concentration, reflecting the mean free drug fraction measured in the population. This parameter was fixed as a uniform distribution in Monte Carlo simulations. For each regimen, the %fT > MIC achieved was determined at the fifth dose (steady-state) for doubling MICs from 1 μg/mL to 64 μg/mL.

Drug costs were evaluated as a secondary outcome using the averaged direct pharmaceutical cost to the hospital of piperacillin/tazobactam ($1.67 per gram). Cost data were provided by the hospital pharmacy. Cost data calculations, provided for purposes of illustrating the financial impact of ARC, excluded personnel and ancillary supply costs.

Statistical Analysis

PK parameter distributions were tested for normality by the Shapiro-Wilk test. Mean or median values were compared using Student's t test or the Wilcoxon rank-sum test, as appropriate. SPSS version 19.0.0 (IBM, Armonk, NY) was used to calculate the area under the ROC curve. JMP version 9.0.0 (SAS Institute, Inc., Cary, NC) was used for all other statistical calculations. HPLC assay variability was assessed by within- and between-day coefficients of variation.

RESULTS

From 83 subjects in both studies, 13 met the criteria for inclusion. The subjects varied in their mechanisms of injury/illness, indication for antimicrobial therapy, age (44.7 [18.6] years), sex (five females, eight males), body weight (79.8 [18.1] kg), body mass index (27.0 [5.2] kg/m^2), admission for trauma (54.0%), and severity of illness as graded by SOFA (5.5 [2.4]) and Acute Physiology and Chronic Health Evaluation II (APACHE II) (15.3 [5.3]) scores on the day of PK sampling. There were no significant differences in these parameters (Table 1 and Supplemental Table 1,

TABLE 2. PK Parameter Estimates for Free Piperacillin and Tazobactam in Patients Stratified by ARC Score of 6 or Lower Versus ARC Score of 7 of Higher

	Free Piperacillin			Free Tazobactam		
	ARC Score ≤ 6 (n = 5)	ARC Score ≥ 7 (n = 8)	p	ARC Score ≤ 6 (n = 5)	ARC Score ≥ 7 (n = 7)	p
Volume of distribution, L/kg	0.37 (0.29–0.52)	1.23 (0.77–2.23)	0.008	0.51 (0.34–0.55)	0.82 (0.73–1.96)	0.007
Clearance, mL/kg/min	2.5 (1.7–4.5)	12.3 (5.3–17.5)	0.003	3.0 (1.9–4.3)	9.7 (4.9–14.6)	0.01
AUC, h·μg/mL	233.9 (176.9–453.0)	76.4 (50.3–101.7)	0.003	29.2 (22.1–44.6)	9.3 (7.2–16.1)	0.007
Peak, μg/mL	80.8 (65.0–157.9)	35.0 (29.2–54.7)	0.003	12.7 (4.6)	5.9 (2.8)	0.03
Trough, μg/mL	11.7 (4.5–28.8)	2.7 (0.8–5.6)	0.11	1.8 (1.1–2.6)	0.3 (0.1–1.1)	0.02

Data are presented as mean (SD) or median (IQR).

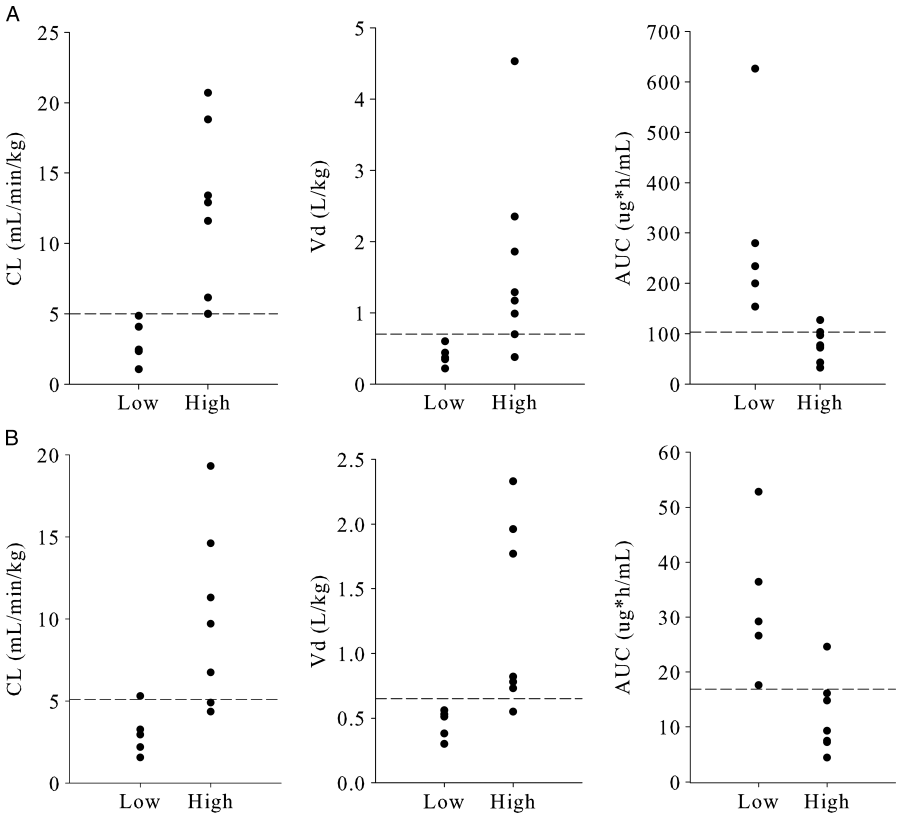

Figure 1. Clearance, volume of distribution, and AUC for free piperacillin (n = 13) (*A*) and free tazobactam (n = 12) (*B*) in patients with ARC scores of 6 or lower (low) and 7 or higher (high). *Dashed line* represents the population median of the low and high ARC score groups combined.

http://links.lww.com/TA/A408). The median ARC scores in low and high score groups were 3 (interquartile range [IQR], 0.5–5) and 9 (IQR, 7–9), with an overall population median of 7 (IQR, 3.5–9). Eight patients (61.5%) had ARC scores of 7 or higher, defining the group at highest risk for ARC. Of these, seven were enrolled from the critical illness study and one from the negative-pressure wound therapy study. Piperacillin therapy was prophylactic, empiric, or culture negative in seven subjects (four with high ARC scores), whereas six subjects received culture-directed therapy for *Escherichia coli*, *Enterobacter* species, or *Citrobacter koseri* infections (four with high ARC scores). All subjects were clinically cured and survived to hospital discharge, with the exception of one subject who had a persistent abscess in the setting of a fistula. There were no adverse events related to PK sampling.

Stratification of patients by ARC risk group distinguished two populations with distinct PK handling of antimicrobials (Table 2, Fig. 1). Weight-adjusted dosing between the two groups was statistically equivalent, with the high ARC score group receiving a higher mean dose (44.0 [24.3] mg/kg vs. 22.1 [26.7] mg/kg, $p = 0.17$). More rapid clearance and larger volumes of distribution were observed among patients with high ARC scores for the free and total drug fractions (total not shown) of

TABLE 3. Diagnostic Performance of the ARC Score for Detecting Altered Pharmacokinetics of Free Piperacillin

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	ROC*
Clearance > median	100.0 (51.7–100.0)	71.4 (30.3–94.9)	75.0 (35.6–95.6)	100.0 (46.3–100.0)	0.86 (0.64–1.0)
Volume of distribution > median	100.0 (51.7–100.0)	71.4 (30.3–94.9)	75.0 (35.6–95.6)	100.0 (46.3–100.0)	0.86 (0.64–1.0)
AUC < median	100.0 (51.7–100.0)	71.4 (30.3–94.9)	75.0 (35.6–95.6)	100.0 (46.3–100.0)	0.86 (0.64–1.0)
<50% *f*T > MIC**	100.0 (51.7–100.0)	71.4 (30.3–94.9)	75.0 (35.6–95.6)	100.0 (46.3–100.0)	0.86 (0.64–1.0)
Clearance > median by SCr < 0.60 mg/dL†	66.7 (24.1–94.0)	71.4 (30.3–94.9)	66.7 (24.1–94.0)	71.4 (30.3–94.9)	0.69 (0.39–0.99)

*Area under the ROC curve.
**Analysis uses an MIC of 16 μg/mL.
†SCr was substituted for ARC score group as the predictive variable.
Parentheses indicate 95% confidence intervals.
SCr, serum creatinine.

piperacillin and tazobactam. These factors may have significantly reduced the antimicrobial exposure, reflected in reduced AUCs compared with patients with low ARC scores (Table 2, Fig. 1).

With the use of the population median as a reference, high ARC scores correctly identified six (75.0%) of eight patients having higher free piperacillin clearance, five (62.5%) of eight having higher volumes of distribution, and five (62.5%) of eight with reduced drug exposure reflected by AUC values. Low ARC scores correctly identified all five patients (100%) with clearance/volumes of distribution greater than and AUC less than the population median.

Sensitivities, specificities, and PPV and NPV were calculated for each of these median-based metrics, showing high sensitivity and NPV and moderate specificity and PPV (Table 3). Diagnostic performance was further evaluated by areas under the ROC curves for the agents together (except tazobactam, which lacks direct antimicrobial activity) as well as for piperacillin alone, showing high accuracy. With the use of the PD criterion of 50% *f*T > MIC, ARC scores were also found to be 100% sensitive for predicting suboptimal drug levels for a bacterial isolate with piperacillin MIC of 16 μg/mL. Finally, for comparison with current practices, the serum creatinine threshold of less than 0.6 mg/dL (the most accurate creatinine criterion by ROC area) was found to have less sensitivity but similar specificity compared with the ARC score. Uncertainties in these estimates were large because of the small sample size (Table 3).

Two subjects with ARC scores between 4 and 6 points (intermediate risk under the original scoring system, revised here to low risk) had *f*T > MIC values of 96.7% and 99.7%

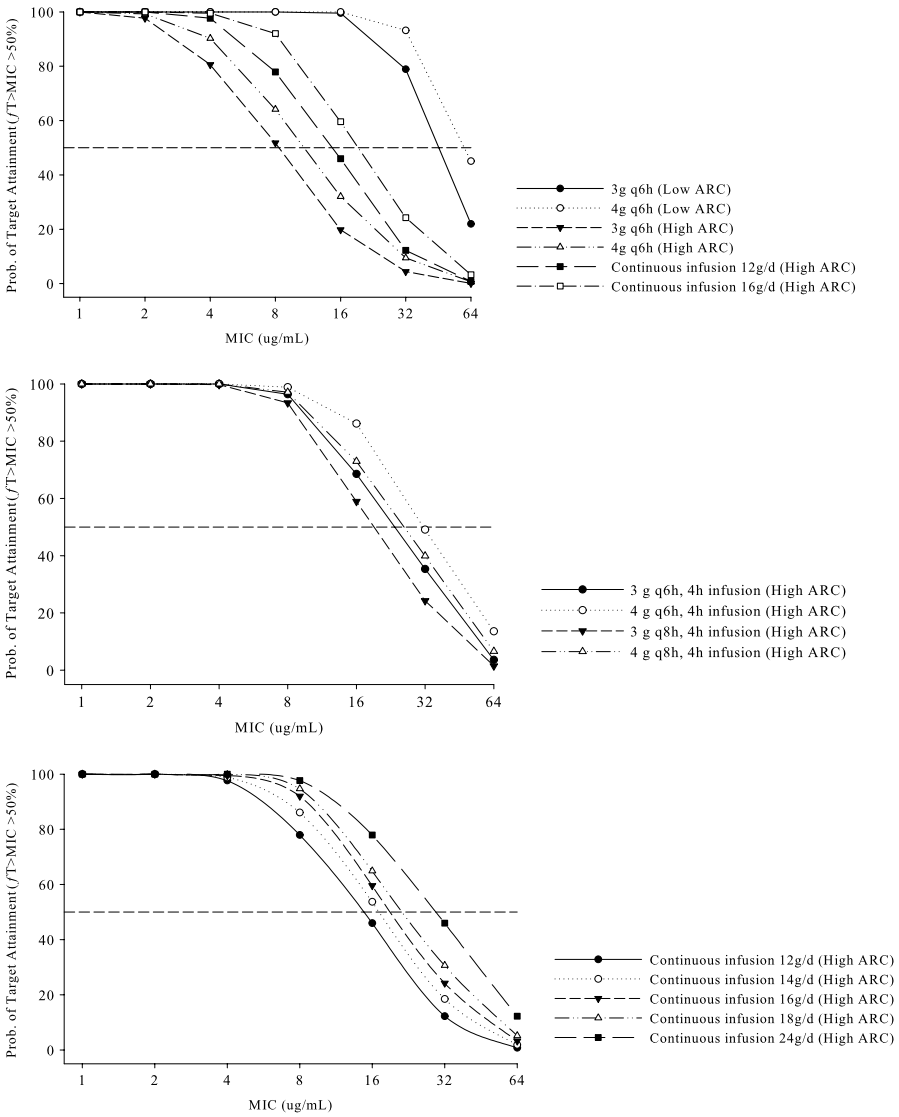

Figure 2. Probability of target attainment for free piperacillin resulting from FDA-approved intermittent doses and continuous infusions. Doses were modeled with median clearance and volume of distribution parameters from subjects having low and high ARC scores.

(for MIC of 16 μg/mL), consistent with other members of the low-risk group. The *f*T > MIC achieved by those with high ARC scores for a range of clinically relevant MIC values was significantly degraded at MICs of 4, 8, 16, and 32 μg/mL compared with those with low ARC scores (Supplemental Table 2, http://links.lww.com/TA/A408). This finding was further supported by Monte Carlo simulations demonstrating that 3-g and 4-g doses every 6 hours failed to achieve *f*T > MIC > 50% for MIC of 16 μg/mL in those with high ARC scores (Fig. 2*A*). Additional simulations directed at finding alternative doses to compensate for the high clearance indicated that extended infusion delivery of at least 12 g/d (500 mg/h) would be sufficient (Fig. 2*B*; Supplemental Table 2, http://links.lww.com/TA/A408), whereas only 4 g to 6 g every 4 hours or 6 g to 8 g every 6 hours (a total of 24–36 g/d) would be required if delivered by intermittent dosing (Fig. 3, Supplemental Table 3, http://links.lww.com/TA/A408). Continuous infusion regimens of 14 g/d or higher were also predicted to be sufficient (Fig. 2*C*; Supplemental Table 3, http://links.lww.com/TA/A408).

Costs associated with therapies having predicted efficacy were evaluated using the mean hospital cost per gram for piperacillin/tazobactam. For high ARC score patients, estimated daily drug costs using extended infusion (12 g/d) would be $20.04, whereas effective intermittently dosed regimens would cost $40.08 (4 g every 4 hours, 6 g every 6 hours), $53.44 (8 g every 6 hours), or $60.12 (6g every 4 hours). Thus, extended infusion would offer drug cost savings of 50.0%, 62.5%, or 66.7%, respectively, while occupying only a single vascular access port and deferring a daily sodium load of 768 mg to 1,536 mg (64-mg/g piperacillin). Cost advantages associated personnel time are not captured in this simplistic analysis, which could ultimately favor continuous infusion therapy.

DISCUSSION

We examined the utility of a simple clinical scoring system to predict ARC in a population of surgical and trauma patients with documented piperacillin pharmacokinetics. Our finding that high ARC scores distinguished a population of patients exhibiting significantly compromised pharmacokinetics suggests that this phenomenon may be silently undermining the efficacy of antimicrobial therapy for patients in our trauma and

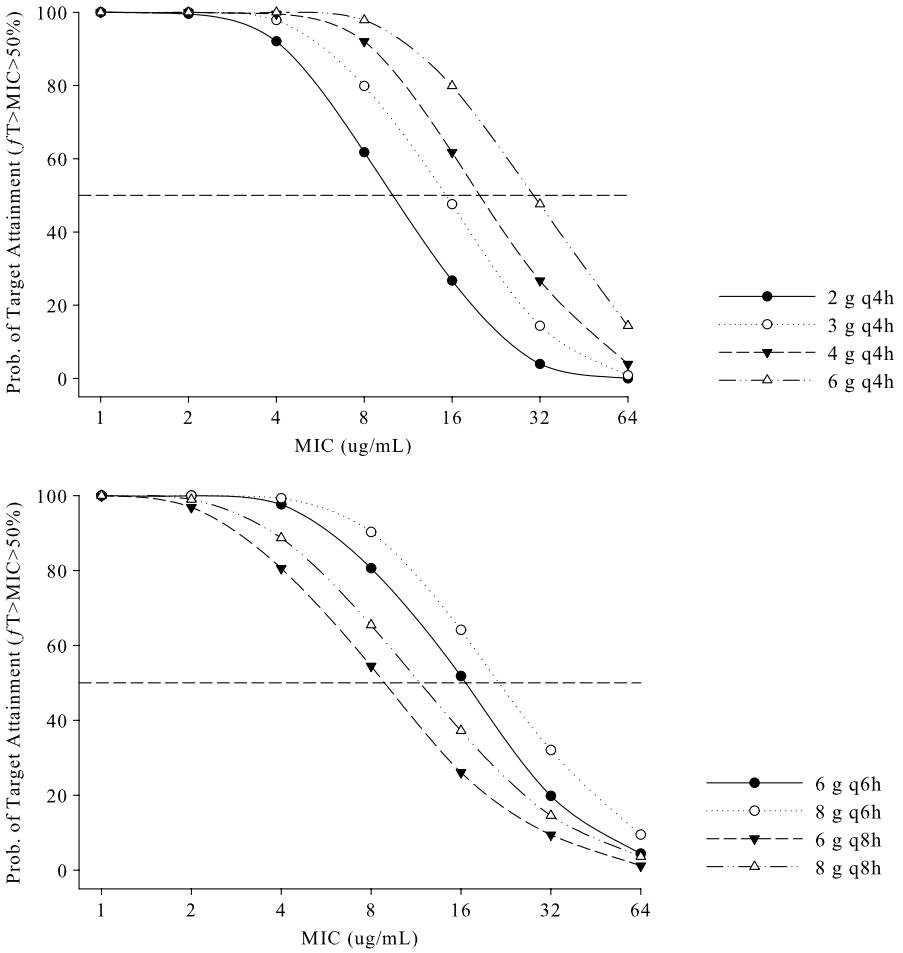

Figure 3. Probability of target attainment for free piperacillin resulting from alternative intermittent dosing regimens using clearance and volume of distribution parameters from patients with high ARC scores. *Dashed line* represents the therapeutic target of 50% free piperacillin time greater than the MIC (*f*T > MIC).

surgical ICUs. Using parameter estimates from this population, we examined potential alternative dosing strategies for patients with high ARC risk scores, which suggested advantages associated with continuous infusion administration in terms of simplicity, efficacy, and cost of treatment for pathogens with MICs up to 16 μg/mL.

Antimicrobial therapy remains, appropriately, a cornerstone of therapy for sepsis. Dosing strategies typically follow Food and Drug Administration (FDA)–approved guidelines established in Phase I to III studies, which include patients selected according to stringent inclusion criteria. However, this minimizes, by design, the reality of interindividual variation in drug disposition. Sources include medical disease of the primary clearance organs (liver and kidneys), resuscitative fluids, hypoalbuminemia, and enhancements to drug clearance from adjunctive therapies such as continuous renal replacement therapy or extracorporeal membrane oxygenation. Recent evidence examining the adequacy of antimicrobial therapy in unselected critically ill or injured patients, particularly those with sepsis, suggests that recommended doses may not meet PK/PD targets associated with optimal bactericidal activity.[1,3] Because only vancomycin and aminoglycoside antibiotic levels are available for routine measurement in clinical practice, the enhanced renal clearance of antimicrobials and other renally cleared medications important to the care of critically ill patients may go unrecognized.

A number of studies, including ours, support the use of extended or continuous infusion dosing to achieve higher concentrations more efficiently than intermittent dosing.[7–12] This is limited by the spontaneous decomposition of some antimicrobial agents at room temperature for a prolonged period. Currently, consensus is lacking on alternative dosing strategies to effectively overcome renal losses due to ARC, which could potentially be exacerbated by extracorporeal therapies (e.g., extracorporeal membrane oxygenation) now used in modern ICU care.[13] A recent study examined extended interval dosing of piperacillin/tazobactam and meropenem, finding it insufficient to overcome clearance-related losses in 37% of patients with ARC.[14] Alternative dosing strategies would constitute off-label use, which may be a concern for some providers. However, our data suggest that standard FDA-approved doses may be insufficient for a subset of patients who are younger, admitted for trauma, and healthy before admission. Considering the demographics of the US military, this describes the majority of expected combat casualties.[6]

This diagnostics study provides Level III evidence via retrospective assignment of ARC scores to prospectively enrolled patients contributing antimicrobial pharmacokinetics data. We observed a very strong statistical signal despite our small sample size, which prevented a meaningful analysis of clinical outcomes. Our study is limited in that we were not able to ascertain retrospectively a diagnosis of ARC by urine creatinine clearance measurement. However, ARC has been observed in 34.3% of 1,786 combined ICU patients,[3–5,14,15] and piperacillin is cleared predominantly by the kidneys, as indicated by recommended dose reductions in renal impairment.[16] Thus, we feel that ARC is the most likely cause of the low antimicrobial levels observed in some of our patients.

Patients in this study were critically ill, enrolled from a surgical/trauma ICU setting, and unselected beyond basic eligibility criteria. The intervention of screening patients with the ARC score is practical, noninvasive, and easily implemented in modern ICU environments, since the elements required to calculate the SOFA score are typically generated during routine care of the most severely ill patients. Positive screening test results (high ARC scores) can be confirmed with the comparator test, a timed urine creatinine concentration from which to determine the glomerular filtration rate. Once the diagnosis of ARC is confirmed, modified antimicrobial dosing can be applied to offset the accelerated clearance, maintaining the PK outcome of $fT > MIC > 50\%$ and, by extension, optimal outcomes in sepsis and bacteremia.

Future studies should confirm, and perhaps improve on, the diagnostic accuracy of the ARC score in prospective trials that measure both ARC and antimicrobial pharmacokinetics, in combination with interventions with alternative dosing strategies that may correct for the dramatic renal losses in these patients. A practical approach for eventual clinical implementation would be to identify ARC by the rate of drug accumulating in the urine from a single measurement from a timed urine collection. This would be advantageous given the challenges of accurate blood sample timing in a clinical ICU environment. A point-of-care technology for rapidly determining concentrations of key antimicrobials, in combination with emerging technologies to rapidly determine MICs,[17] would be helpful to bring personalized antimicrobial prescriptions to the ICU bedside. Some approaches meriting further investigation include enzyme thermisters[18] using immobilized β-lactamase enzymes and impedance spectroscopy using antibody-mediated capture of low molecular weight drugs.[19]

CONCLUSION

Rapid antimicrobial clearance occurs in a subpopulation of surgical and trauma ICU patients and can potentially compromise therapeutic efficacy. The ARC score was highly sensitive and moderately specific at identifying patients at risk. Simulation data suggest a potential role for overcoming this rapid clearance through the use of continuous infusion dosing. Adequately powered prospective studies are needed to confirm its utility and determine suitable dose adjustments to compensate for the rapid antimicrobial clearance that can occur in surgical and trauma ICU patients.

AUTHORSHIP

K.S.A., J.M.C. and C.K.M. provided the study design. K.L.N. performed the data acquisition. K.S.A. and J.M.C. performed the data analysis and interpretation. All authors contributed in the drafting of the manuscript and critical revision.

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DISCLOSURE

This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol H-09-059.

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